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(54) Title: COMBINATION THERAPY FOR TREATING DISEASE

(57) Abstract: Disclosed are methods for treating cancer comprising administering a xenotypic monoclonal antibody and a chemotherapeutic drug to a patient suffering from cancer. Also disclosed is a method for inducing a host immune response in a patient against a multi-epitopic in vivo tumor antigen in present in the host serum, which antigen does not elicit a host immune response, comprising administering to the patient a chemotherapeutic drug and a composition comprising a binding agent that specifically binds to a first epitope on the antigen and allowing the binding agent to form a binding agent/antigen pair, wherein a host immune response is elicited against a second epitope on the antigen.

COMBINATION THERAPY FOR TREATING DISEASE

(Atty Docket Number ALT-013PC)

BACKGROUND OF THE INVENTION

Field of the invention

The invention relates to immunology. More particularly the invention relates to the use of immunotherapy in combination with chemotherapy.

Summary of the Related Art

Despite the progress that modern medicine has made in treating cancer, cancer recurrence remains a concern. For a majority of cancers, typical treatment includes surgery followed by high doses of chemotherapy. A majority of these patients relapse and do not respond to other chemotherapeutic treatments. These patients then avail themselves to experimental or salvage treatments.

Current experimental regimens focus on mixing chemotherapies in an attempt to overcome resistance issues. Most of these treatments result in serious blood toxicities such as neutropenia, and thrombocytopenia. Other serious and frustrating symptoms to the patient include hair loss and nausea. Researchers are now looking at ways to enhance the immune system through less toxic means while still eliminating the cancer.

Many have turned to the use of chemotherapy in conjunction with antibody treatments. Many of these have also presented similar toxicities to the chemotherapy.

Thus, there remains a need to identify new treatments that not only treat the initial symptoms of a disease, but also alleviate and/or prevent recurrence of those symptoms.

BRIEF SUMMARY OF THE INVENTION

In a first aspect the invention provides a method for treating cancer, comprising concurrently administering xenotypic monoclonal antibody and a chemotherapeutic drug to a patient suffering from cancer. Preferably the patient is human.

In a second aspect the invention provides a method for treating cancer, comprising surgical removal of the cancer, concurrent administration of a chemotherapeutic drug and a xenotypic monoclonal antibody in a dose equal to or less than 2mg.

In a third aspect, the invention provides a method for treating cancer, comprising surgical removal removal of the cancer, administration of a xenotypic monoclonal antibody on weeks 1, 3, 5, 9, followed by concurrent administration of a chemotherapeutic drug and a xenotypic monoclonal antibody on week 12 in a dose equal to or less than 2mg.

In a fourth aspect, the invention provides a method for inducing a host immune response in a patient against a multi-epitopic in vivo tumor antigen, which antigen does not elicit an effective host immune response, comprising concurrently administering to the patient a chemotherapeutic drug and a composition comprising a binding agent that specifically binds to a first epitope on the antigen and allowing the binding agent to form a binding agent/antigen pair, wherein a host immune response is elicited against a second epitope on the antigen.

In a fifth aspect, the invention provides a method for treating cancer, comprising concurrent administration of a chemotherapeutic drug, a binding agent, and an antigen.

In a sixth aspect, the invention provides method for inducing a host immune response in a patient against a multi-epitopic in vivo tumor antigen, which antigen does not elicit an effective host immune response, comprising concurrently administering to the patient a chemotherapeutic drug and a composition comprising a binding agent present in an amount of from 0.1μg to 2mg per kg of body weight of the host, and wherein the binding agent specifically binds to an epitope on the antigen and an effective host immune response is elicited against a second epitope on the antigen.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a table showing the results of three clinical studies where Alt-2 is administered concurrently with a chemotherapeutic drug.

Figure 2 is a diagram showing a non-limiting embodiment of the invention.

Figure 3 is a graph showing the difference in the numbers between Ab2 responders (white squares) (effective immune response) and Ab2 non-responders (black sqûares)(ineffective immune response) with time.

Figure 4 is a table showing the different disease characteristics of Ab2 responders and Ab2 non-responders.

DETAILED DESCRIPTION

The present invention stems from the discovery that a combination of immunotherapy with traditional chemotherapy and/or radiotherapy alleviates and/or prevents the recurrence of cancer. The presence of a host anti-xenotypic antibody response in a patient will stimulate an immune response. The inventors have exploited this discovery to develop therapeutics containing binding agents useful in immunotherapy and chemotherapeutic or radiotherapeutic drugs, as well as methods for using these therapeutics. The patents and publications cited herein reflect the level of skill in this field and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of any conflict between a cited reference and this specification, this specification shall prevail.

Accordingly in a first aspect the invention provides a method for treating cancer, comprising concurrently administering xenotypic monoclonal antibody and a chemotherapeutic drug to a patient suffering from cancer. In some embodiments of the invention, the binding by the xenotypic monoclonal antibody of a first single epitope exposes a second distinct epitope on the antigen. In some embodiments of the invention, the xenotypic monoclonal antibody, when bound to the antigen, forms an immunogenic complex. Exemplary xenotypic monoclonal antibodies ("MAb"), preferably include IgG1 antibodies; chimeric monoclonal antibodies ("C-MAb"); humanized antibodies; genetically engineered monoclonal antibodies ("G-MAb"); fragments of monoclonal antibodies (including but not limited to "$F(Ab)_2$", "F(Ab)" and "Dab"); and single chains representing the reactive portion of monoclonal antibodies ("SC-MAb"). The binding agent may be labeled or unlabeled.

Where the patient is human, preferred xenotypic monoclonal antibodies include, without limitation, murine monoclonal antibodies. Particularly preferred murine monoclonal antibodies include Alt-1 (murine IgG1, specifically binds to MUC-1; ATCC No. PTA-975; American Type Culture Collection, Manassas, VA),

Alt-2 (OvaRex® MAb B43.13, murine IgG1, specifically binds to CA125; ATCC No. PTA-1883), Alt3 (murine IgG3, specifically binds to CA19.9; ATCC No. PTA-2691), Alt-4 (murine IgM, specifically binds to CA19.9; ATCC No. PTA-2692), Alt-5 (murine IgG1, specifically binds to CA19.9; ATCC No. PTA-2690); and Alt-6 (murine IgG1, specifically binds to prostate specific antigen (PSA); ATCC No. HB-12526).

The methods according to the invention are useful for providing a therapeutic benefit to patients suffering from cancer. As used herein, the term "cancer" is used to mean a condition in which a cell in a patient's body undergoes abnormal, uncontrolled proliferation. The abnormal cell may proliferate to form a solid tumor, or may proliferate to form a multitude of cells (*e.g.*, leukemia). Note that because cancer is the abnormal, uncontrolled proliferation of a patient's cell, the term does not encompass the normal proliferation of a cell, such as a stem cell or a spermatocyte.

By "treating a patient suffering from cancer" is meant that the patient's symptoms are alleviated following treatment according to the invention. In one non-limiting example, a patient suffering from a highly metastatic cancer (e.g., breast cancer) is treated where additional metastasis either do not occur, or are reduced in number as compared to a patient who does not receive treatment. In another non-limiting example, a patient is treated where the patient's solid cancer either becomes reduced in size or does not increase in size as compared to a patient who does not receive treatment. In yet another non-limiting example, the number of cancer cells (*e.g.*, leukemia cells) in a treated patient either does not increase or is reduced as compared to the number of cancer cells in a patient who does not receive treatment. In preferred embodiments the patient is human.

It will be appreciated that a "patient suffering from cancer" of the invention may express the mutant protein and not yet be symptomatic for the disease. For example, where the cancer is colon cancer (which is associated with the mutant K-ras protein), a patient with a mutant K-ras protein in some cells of the colon is a patient

according to the invention even though that patient may not yet be symptomatic for colon cancer. "Associated with a mutant protein" means signs or symptoms of illness in a majority of patients are present when the mutant protein is present in the patient's body, but in which signs or symptoms of illness are absent when the mutant protein is absent from the patient's body. "Signs or symptoms of illness" are clinically recognized manifestations or indications of disease.

Preferably, the therapeutic compositions of the invention further comprise a pharmaceutically acceptable carrier. By "pharmaceutically acceptable carrier" is meant a carrier that is physiologically acceptable to the administered patient. One exemplary pharmaceutically acceptable carrier is physiological saline. Other pharmaceutically-acceptable carriers and their formulations are well-known and generally described in, for example, Remington's pharmaceutical Sciences (18^{th} Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990)

"Administering" as used herein means providing the composition to the patient in a manner that results in the composition being inside the patient's body. Such an administration can be by any route including, without limitation, parenteral, sub-cutaneous, intradermal, intravenous, intra-arterial, intraperitoneal, and intramuscular.

In certain embodiments of the invention, the chemotherapeutic drug used is commercially available. Some non limiting examples include carboplatin, cisplatin, docetaxel, paclitaxel, doxorubicin, HCl liposome injection, topotecan, hydrochloride, gemcitabine, cyclophosphamide, and etoposide or any combination thereof.

In preferred embodiments the chemotherapeutic drug is administered within a week before or after the murine monoclonal antibody.

In a second aspect the invention provides a method for treating cancer, comprising surgery, administration of a chemotherapeutic drug, administration of a xenotypic monoclonal antibody in a dose equal to or less than 2mg given by

intravenous infusion over 20 minutes during weeks 1, 3, 5, 9, then every 8 weeks, followed by administration of a chemotherapeutic drug within 5 days of the administration of the binding agent.

In certain, non-limiting embodiments of the invention, the xenotypic antibody, e.g. Alt-2 is administered as a 2 mg dose dissolved in 50 mL saline and infused slowly preferably over approximately 20 minutes. If an allergic or other reaction occurs that may limit the completion of the dose, then a lower dose may be employed at that time or with subsequent treatments, so that the expected dose range would be 1-2 mg per treatment. Premedication with oral or intravenous dyphenhydramine 25 to 50 mg is usually administered to lessen the risk of allergic reaction to the protein. The schedule used for combined Alt-2 and chemotherapy comprises administering Alt-2 at the dose above at weeks 1, 3, 5, 7, 9 with chemotherapy administered with Alt-2 on weeks 12 through 26. Alt-2 may be started after recovery from any required surgery that is done prior to the chemotherapy, and then continued up to and during the chemotherapy treatment period. The chemotherapy can be given in 3-4 week cycles or other schedules according to the treating physician and common clinical practice. Chemotherapy may continue for up to six cycles followed by the xenotypic antibody administration every twelve weeks for up to two years.

In a third aspect the invention provides a method for treating cancer, comprising surgery, followed within seven days by administration of a xenotypic monoclonal antibody in a dose equal to or less than 2mg given by intravenous infusion over 20 minutes during weeks 1, 3, 5, 9, then every 8 weeks with concurrent administration of a chemotherapeutic drug on week 3 and thereafter.

In another non-limiting example the murine antibody is administered at week 1 after completing standard surgery but has not yet begun chemotherapy. The murine antibody is administered in a dose equal to or less than 2mg through a 20 minute intravenous infusion followed by a second treatment and concurrent administration of a chemotherapeutic drug on weeks 6 and beyond. "Concurrent Administration"

means administration within a relatively short time period from each other. Preferably such time period is less than 2 weeks, more preferably less than 7 days, most preferably less than 1 day and could even be administered simultaneously.

The expected progression-free survival times may be measured in months to years, depending on prognostic factors including the number of relapses, stage of disease, and other factors. Overall survival is also measured in months to years. In the case of ovarian cancer, the addition of the xenotypic monoclonal antibody, Alt-2 is expected to increase the time to recurrence or progression, and may also prolong the survival time. Any improvement of 2 months or longer is usually considered to be clinically meaningful.

In a fourth aspect, the invention provides a method for inducing a host immune response in a patient against a multi-epitopic in vivo tumor antigen in present in the host serum, which antigen does not elicit a host immune response, comprising administering to the patient a chemotherapeutic drug and a composition comprising a binding agent that specifically binds to a first epitope ton the antigen and allowing the binding agent to form a binding agent/antigen pair, wherein a host immune response is elicited against a second epitope on the antigen. Exemplary multi-epitopic antigens are described in and herein incorporated by reference in Nicodemus C.F. et al, Expert Rev. Vaccines 1(1), 34-48 (2002), Qi et al, Hybridoma and Hybridomics 20, 313-323 (2001), and Berlyn et al., Clin. Immunol. 101, 276-283, (2001).

A "binding agent", as used herein, refers to one member of a binding pair, including an immunologic pair, *e.g.*, a binding moiety that is capable of binding to an antigen, preferably a single epitope expressed on the antigen, such as a pre-determined tumor antigen. In some embodiments of the invention, the binding of a first single epitope exposes a second distinct epitope on the antigen. In some embodiments of the invention, the binding agent, when bound to the antigen, forms an immunogenic complex. Exemplary binding agents include, but are not limited to: antibodies, monoclonal antibodies ("MAb"), preferably IgG1 antibodies; chimeric

monoclonal antibodies ("C-MAb"); humanized antibodies; genetically engineered monoclonal antibodies ("G-MAb"); fragments of monoclonal antibodies (including but not limited to "$F(Ab)_2$", "F(Ab)" and "Dab"); single chains representing the reactive portion of monoclonal antibodies ("SC-MAb"); antigen-binding peptides; tumor-binding peptides; a protein, including receptor proteins; peptide; polypeptide; glycoprotein; lipoprotein, or the like, e.g., growth factors; lymphokines and cytokines; enzymes, immune modulators; hormones, for example, somatostatin; any of the above joined to a molecule that mediates an effector function; and mimics or fragments of any of the above. The binding agent may be labeled or unlabeled.

Preferred binding agents of the invention are monoclonal antibodies. Where the patient is human, these xenotypic monoclonal antibodies include, without limitation, murine monoclonal antibodies. Particularly preferred murine monoclonal antibodies include Alt-1 (murine IgG1, specifically binds to MUC-1; ATCC No. PTA-975; American Type Culture Collection, Manassas, VA), Alt-2 (OvaRex® MAb B43.13, murine IgG1, specifically binds to CA125; ATCC No. PTA-1883), Alt3 (murine IgG3, specifically binds to CA19.9; ATCC No. PTA-2691), Alt-4 (murine IgM, specifically binds to CA19.9; ATCC No. PTA-2692), Alt-5 (murine IgG1, specifically binds to CA19.9; ATCC No. PTA-2690); and Alt-6 (murine IgG1, specifically binds to prostate specific antigen (PSA); ATCC No. HB-12526).

A "multi-epitopic in vivo tumor antigen" is an antigen that present multiple epitopes on its surface. Some non-limiting examples of such antigens include CA125, MUC-1, PSA, CA19.9, and TAG-72.

"Inducing a host immune response" means that the patient experiences alleviation or reduction of signs or symptoms of illness, and specifically includes, without limitation, prolongation of survival. In certain preferred embodiments of the methods according to the invention, a CD8+ IFN-γ producing T cell is activated to induce a cytotoxic T lymphocyte (CTL) immune response in the patient administered the murine monoclonal antibody. In certain embodiments of the methods according

to the invention, a CD4+ IFN-γ producing T cell is activated to induce a helper T cell immune response in the patient administered with the composition. These activated CD4+IFN-γ producing T cells (i.e., helper T cells) provide necessary immunological help (e.g. by release of cytokines) to induce and maintain not only CTL, but also a humoral immune response mediated by B cells. Thus, in certain embodiments of the methods according to the invention, a humoral response to the antigen is activated in the patient administered with the composition.

Activation of a CD8+ and/or CD4+ IFN-γ producing T cells means causing T cells that have the ability to produce IFN-γ to actually produce IFN-γ, or to increase their production of IFN-γ. "Induction of CTL" means causing potentially cytotoxic T lymphocytes to exhibit antigen specific cytotoxicity. "Antigen specific cytotoxicity" means cytotoxicity against a cell presenting an antigen that is associated with the antigen associated with the cancer that is greater than an antigen that is not associated with the cancer. "Cytotoxicity" refers to the ability of the cytotoxic T lymphocyte to kill the target cell. Preferably, such antigen-specific cytotoxicity is at least 3-fold, more preferably 10-fold greater, more preferably more than 100-fold greater than cytotoxicity against a cell not presenting the antigen not associated with the cancer.

In a fifth aspect, the invention includes a method for treating cancer, comprising concurrent administration of a chemotherapeutic drug, a binding agent, and an antigen.

In a sixth aspect, the invention provides a method for inducing a host immune response in a patient against a multi-epitopic in vivo tumor antigen, which antigen does not elicit an effective host immune response, comprising concurrently administering to the patient a chemotherapeutic drug and a composition comprising a binding agent present in an amount of from 0.1 μg to 2mg per kg of body weight of the host, and wherein the binding agent specifically binds to an epitope on the antigen and an effective host immune response is elicited against a second epitope on the antigen.

Example I

Clinical and Immunologic Outcomes of Patients with Recurrent Epithelial Ovarian Cancer (EOC) treated with B43.13 and Chemotherapy (Ct)-- Interim immunology and clinical results from study OVA-Gy-12.

Patients with recurrence after platinum therapy and a first surgery and were enrolled if they were candidates for secondary surgery and continued chemotherapy. Alt-2 was administered by 20-minute infusion in weeks 1, 3, 5, and 9 prior to initiation of chemotherapy, and then an option to continue every 8 weeks x 2 doses concurrent with chemotherapy on weeks 12 and 26. Humoral immune responses, including HAMA, Ab2 and anti-CA125 antibody, were assessed at baseline and serially. Using gamma-interferon ELISPOT assay, T cell responses were evaluated for activation by Alt-2, CA125, or autologous tumor.

20 patients were enrolled; median follow-up was 6 months ranging up to 2 years. Alt-2 was well tolerated and did not produce drug-related serious adverse reactions. In 14 of 19 (71%) evaluable patients, robust treatment-emergent humoral responses were observed to the constant (HAMA) and variable region of the antibody (Ab2). To date, 5 of 8 (62.5%) patients tested demonstrated functionally active T cells, stimulated by CA125 or by autologous tumor. T cell responses to Alt-2 were demonstrated in 4 patients. T cell responses were MHC class I and II restricted, indicating the activation of CTL (cytotoxic T lymphocytes) and T helper cells. Immune responses were commonly induced by wk 12 after 4 doses, and were generally maintained in patients continuing combined treatment with Alt-2 and chemotherapy. 75% are still alive and median survival has not been reached at 120 weeks.

Conclusions: Alt-2 is well tolerated and induces multiple antigen-specific immune responses, even when combined with chemotherapy. In advanced EOC, these data are among the first to demonstrate induction of tumor-specific T cells.

We claim:

1. A method for treating cancer, comprising concurrently administering xenotypic monoclonal antibody and a chemotherapeutic drug to a patient suffering from cancer.

2. The method of claim 1, wherein the xenotypic monoclonal antibody is murine.

3. The method of claim 2, wherein the antibody is selected from the group consisting of Alt-1, Alt-2, Alt-3, Alt-4, Alt-5, and Alt-6.

4. The method of claim 1, wherein the patient is human.

5. The method of claim 1 or 3, wherein the chemotherapeutic is administered within a week before the murine monoclonal antibody.

6. The method of claim 1or 3 wherein, the chemotherapeutic is administered within a week after the monoclonal antibody.

7. The method of claim 1 or 3, wherein the antibody is administered in a dose of less than or equal to 2mg.

8. The method of claim 2, further comprising surgical removal of the cancer.

9. A method for treating cancer, comprising surgical removal of the cancer, concurrent administration of a chemotherapeutic drug and administration of a xenotypic monoclonal antibody in a dose equal to or less than 2mg.

10. The method of claim 9 wherein the monoclonal antibody is selected from the group consisting of Alt-1, Alt-2, Alt-3, Alt-4, Alt-5, and Alt-6.

11. The method of claim 9 wherein the administration of the antibody is over a 20 minute intravenous infusion.

12. The method of claim 9 wherein the chemotherapeutic drug is administered within seven days prior to the administration of the monoclonal antibody.

13. The method of claim 9 wherein the chemotherapeutic drug is administered within seven days following the administration of the monoclonal antibody.

14. The method of claim 12 or 13 wherein the chemotherapeutic drug is administered every four weeks for six cycles.

15. The method of claim 14 wherein the method further comprises the step of administration of the xenotypic monoclonal antibody every twelve weeks for up to two years.

16. The method of claim 15 wherein the xenotypic monoclonal antibody and chemotherapeutic drug are administered on weeks 1, 4, and 8, followed by further administration of the chemotherapeutic drug alone on weeks 12 and 16, followed by concurrent administration of the chemotherapeutic drug and xenotypic monoclonal antibody on week 20.

17. The method of claim 9 wherein the concurrent administration of the xenotypic monoclonal antibody and the chemotherapeutic drug occurs on week 1, followed by administration of the chemotherapeutic drug on week 4, repeated for six cycles and followed by administration of the xenotypic monoclonal antibody every twelve weeks for up to two years.

18. A method for treating cancer in a patient, comprising surgical removal of the cancer, administration of a xenotypic monoclonal antibody on weeks 1, 3, 5, 7 and 9 followed by concurrent administration of a chemotherapeutic drug and a xenotypic monoclonal antibody in a dose less than or equal to 2mg on week 12.

19. The method of claim 13 wherein the concurrent administration of the chemotherapeutic drug and xenotypic monoclonal antibody is repeated every four weeks for up to 6 cycles.

20. The method of claim 14 further comprising the step of administering the xenotypic monoclonal antibody every twelve weeks for up to two years.

21. The method of claim 11 wherein the monoclonal antibody is selected from the group consisting of Alt-1, Alt-2, Alt-3, Alt-4, Alt-5, and Alt-6.

22. A method for inducing a host immune response in a patient against a multi-epitopic in vivo tumor antigen, which antigen does not elicit an effective host immune response, comprising concurrently administering to the patient a chemotherapeutic drug and a composition comprising a binding agent that specifically binds to a first epitope on the antigen and allowing the binding agent to form a binding agent/antigen pair, wherein a host immune response is elicited against a second epitope on the antigen.

23. The method of claim 22 wherein the xenotypic monoclonal antibody is murine.

24. The method of claim 23, wherein the antibody is selected from the group consisting of Alt-1, Alt-2, Alt-3, Alt-4, Alt-5, and Alt-6.

25. The method of claim 22, wherein the patient is human.

26. The method of claim 22, wherein the chemotherapeutic drug is administered within a week before the murine monoclonal antibody.

27. The method of claim 22, wherein the chemotherapeutic drug is administered within a week after the monoclonal antibody.

28. The method of claim 22, wherein the antibody is administered in a dose of equal to or less than 2mg.

29. The method of claim 22, further comprising surgical removal of the cancer.

30. A method for treating cancer, comprising concurrent administration of a chemotherapeutic drug, a binding agent, and an antigen.

31. The method of claim 30, wherein the binding agent is a murine monoclonal antibody.

32. The method of claim 30, wherein the antibody is selected from the group consisting of Alt-1, Alt-2, Alt-3, Alt-4, Alt-5, and Alt-6.

33. The method of claim 30, wherein the patient is human.

34. The method of claim 31, wherein the chemotherapeutic is administered within a week before the murine monoclonal antibody.

35. The method of claim 31 wherein, the chemotherapeutic is administered within a week after the monoclonal antibody.

36. The method of claim 31, wherein the antibody is administered in a dose of equal to or less than 2mg.

37. A method for inducing a host immune response in a patient against a multi-epitopic in vivo tumor antigen, which antigen does not elicit an effective host immune response, comprising concurrently administering to the patient a chemotherapeutic drug and a composition comprising a binding agent present in an amount of from 0.1μg to 2mg per kg of body weight of the host, and wherein the binding agent specifically binds to an epitope on the antigen and an effective host immune response is elicited against a second epitope on the antigen.

CHEMOTHERAPY/IMMUNOTHERAPY COMBINATIONS

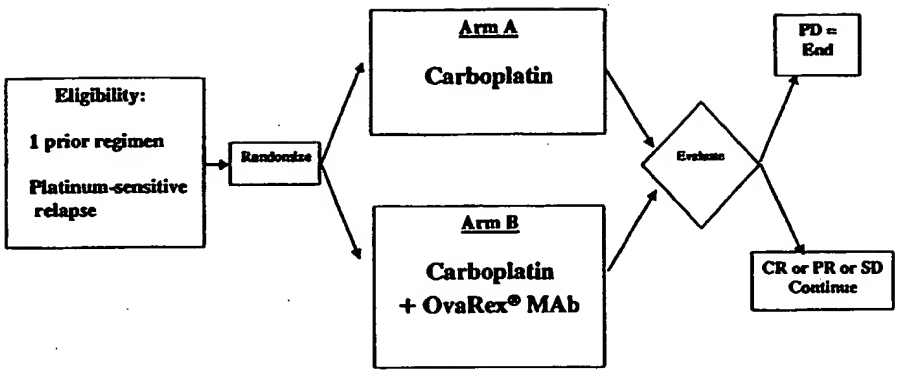
OvaRex® MAb + Salvage Chemotherapy

Chemo	Study No.	Pts	Responses to chemo	Immune response
Carbo, Cis, Pac, Topo, Doxil, Gem, Doc, Cyt, Etop	10	34	Yes	Yes
Carbo, Topo, Gem, Etop	08	7	Yes	N.A.
Carbo, Cis, Pac, Doxil	12	6	Yes	Yes

- Clinical experience in 3 studies
- More data emerging from Study 12 (20 pts treated)
- Encouraging clinical and immune responses esp. CR & PRs with carboplatin and other agents in salvage setting

Cancer Therapy

Figure 1



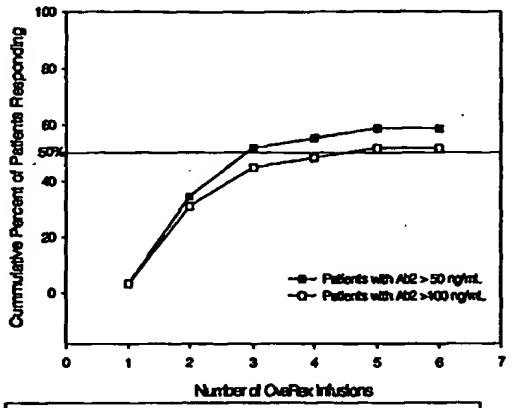
Pts can continue chemotherapy up to 6 cycles and OvaRex® up to 2 yrs.
Endpoints: Time to progression, QOL, Safety, Survival

Figure 2

AB2 RESPONSE AND RELATIONSHIP TO # OF INFUSIONS

Controlled Phase II (Study OVA-Gy-10)

Ab2 Response Vs. No. of Infusions



> 50% immune responders by week 9

Figure 3

Evidence for Drug Effect in Ab2 Responders
Disease characteristics of Ab2 responders vs. nonresponders

Study OVA-Gy-10

	Ab2 ≥ 100 N (%)	Ab2 < 100 N (%)
FIGO IIIC or IV	10 (71)	11 (85)
$TN_{(1)}M$ or $TNM_{(1)}$	9 (53)	1 (8)
Tumor Grade 3	12 (80)	6 (46)
ECOG ≥ 1	6 (38)	6 (46)
Malignant ascites	8 (53)	7 (58)
Staging lap residual >1 cm or not specified	6 (38)	6 (46)
Baseline CA125 ± SD	188 ±170	*279 ±281

*No statistical difference compared to placebo or to pts with Ab2≥100.

Figure 4